

**REMARKS**

Claims 1-5 are pending and await further action on the merits.

New claim 4 is essentially identical to claim 1 except new claim 4 recites that the mirtazapine is “unlabeled”. Support for this feature can be found in the entire disclosure of the specification. Labeled compounds are uncommon and can be used in binding experiments. They are typically not used in treatment. The inventive compounds are taught to be useful for treatment of such diseases as depression. As such, the skilled artisan would reasonably conclude that the present disclosure relates to unlabeled mirtazapine compounds.

New claim 5 is essentially identical to claim 4 except that new claim 5 recites that the melting point of the crystals is 114-116°C. Support for this melting point range can be found in Example 7. No new matter has been added by way of the above-amendment.

**Opposition of Related European Patent**

The present application is in the same patent family as EP 1225174 which is currently undergoing prosecution of an Opposition. Attached hereto for the Examiner’s review is a copy of “Additional Experiment of Example 1, process 4 of P9” which was filed on September 29, 2005 with the European Patent Office during prosecution of the Opposition. The Examiner will note that reference “P9” relates to van der Burg US 4,062,848 which was made of record in the December 24, 2003 IDS.

The experimental evidence shows that Example 1 of van der Burg was essentially repeated and the crystals were shown to have a water content outside the inventive range of “not more than 0.5% by weight” and a hygroscopic degree outside the inventive range of “not more than 0.6% by weight” when the crystals are dried in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours.

The Examiner is kindly requested to acknowledge consideration of the enclosed copy of the submission made during opposition at the EPO by signing and initialing the enclosed PTO/SB/08 form which lists the experimental example.

Issues under 35 U.S.C. 102(b)

The Examiner has maintained the rejection of claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Kaspersen et al. (Journal of Label. Comp. and Radiopharm., Vol. 27, No. 9, 1055, 1989). Applicants respectfully traverse the rejection.

Applicants now respond to the Examiner's comments made in the November 25, 2005 Advisory Action.

Beginning in the first full paragraph of page 4 of the November 25, 2005 Advisory Action, the Examiner responds to Applicants' arguments regarding the hemihydrate. The Examiner has taken the position that this argument is not relevant since Applicants are not claiming a hemihydrate. In response, it appears that the Examiner has misunderstood Applicants' arguments regarding the hemihydrate. Applicants were simply referring to the final compound of Kaspersen et al. as likely being a hemihydrate. It is not Applicants' position that the inventive claims are distinct because a hemihydrate is formed.

The Examiner has maintained the position that Applicants are required to repeat the experiments of Kaspersen et al. to show that the mirtazapine crystals of Kaspersen et al. do not have (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed. Applicants respectfully submit that Applicants have repeated the experiments of Kaspersen et al. to the extent that it is possible.

It is Applicants' position that Example 8 in the present specification is sufficiently close to the description of Kaspersen et al., so that the skilled artisan would come to the reasonable conclusion that the mirtazapine crystals of Kaspersen et al. do not have (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed.

The workup of Kaspersen et al. is as follows:

The product was extracted with ethyl acetate, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield 950 mg (85%) of crude 1c. The crude 1c was purified by chromatography over Alox B (eluted with hexane/ethyl acetate 7:3, v/v) to yield 830 mg. For the final purification the product was treated twice with 100 mg of charcoal in n-hexane (containing 1% of methanol) followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colourless crystals, m.p. 123,8-125,8 °C. No impurities were detectable either on TLC, HPLC or GC.

This workup shows that the final crystals were formed by crystallization. However, there is no discussion by Kaspersen et al. of how the final crystals are dried. The skilled artisan would reasonably conclude that the crystals are dried under "ordinary conditions", since there is no suggestion in the entire disclosure of Kaspersen et al. that the crystals would be dried using conditions which are out of the ordinary. As such, it is appropriate for the Examiner to rely on the experimental data of Example 8 in the present specification to show the properties of the final mirtazapine crystals of Kaspersen et al. and for the Examiner to rely on the experimental data of Example 7 in the present specification to show the properties of the final mirtazapine crystals of the present invention which are dried under relatively stringent conditions.

The product of Example 8 has a water content of about 3.5 % by weight, which is outside the inventive range of water content of "not more than 0.5% by weight". Since the product of Kaspersen et al. is also dried under ordinary conditions, it follows that the product of Kaspersen et al. has a water content of about 3.5 % by weight. Thus, Example 8 of the present specification

is relevant to show that it is likely that the product of Kaspersen et al. is outside the inventive range of water content of "not more than 0.5% by weight".

At page 4 of the November 3, 2005 Amendment, Applicants cited the teachings of "Extract from Hunnius Pharmazeutisches Wörterbuch," 8th Edition, de Gruyter 1998, page 682, (hereinafter "Extract") which has already been filed with the U.S.P.T.O. in the November 23, 2004 IDS. This reference was used to support Applicants' arguments that it is very likely that Kaspersen et al. dried their crystals under "ordinary conditions" to avoid destruction of the crystal.

Specifically, the Extract discloses as follows:

"Water of hydration: Water as a structural element of the crystal lattice of a substance; due to the strong fixation removal of the water of hydration is only possible by higher temperatures with destruction of crystal." (Emphasis added).

With this knowledge of the fragility of crystals to heat, it cannot be expected that Kaspersen et al. would have used high temperatures as was used in Example 7 (90-95°C at 1330-1862 Pa) in the present specification. Certainly, if Kaspersen et al. had used temperatures, such as 90-95°C to dry the crystals, Kaspersen et al. would have described this fact in the experimental section.

Accordingly, the data from Example 8 of the present specification is relevant to show the properties of the product of Kaspersen et al. which was dried under ordinary conditions.

Based on the foregoing, Applicants respectfully submit that the mirtazapine crystals of Kaspersen et al. do not inherently have (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed. As such, withdrawal of the rejection is respectfully requested.

Conclusion

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Garth M. Dahlen, Ph.D., Esq. (Reg. No. 43,575) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

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